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Interventions for orbital lymphangioma (Review)

Patel SR, Rosenberg JB, Barmettler A

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TABLE OF CONTENTS

[Intervention Review]

Interventions for orbital lymphangioma

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ABSTRACT

Background

Orbital lymphangiomas are a subset of localized vascular and lymphatic malformations, which most commonly occur in the head and neck region. Orbital lymphangiomas typically present in the first decade of life with signs of ptosis, proptosis, restriction of ocular motility, compressive optic neuropathy, and disfigurement. Therefore, early and effective treatment is crucial to preserving vision. Due to proximity to vital structures, such as the globe, optic nerve, and extraocular muscles, treatment for these lesions is complicated and includes a large array of approaches including observation, sclerotherapy, systemic therapy, and surgical excision. Of these options, there is no clear gold standard of treatment.

Objectives

To assess the evidence supporting medical and surgical interventions for the reduction/treatment of orbital lymphangiomas in children and young adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 5); Ovid MEDLINE; Embase.com; PubMed; Latin American and Caribbean Health Sciences Literature Database (LILACS); ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We did not use any date or language restrictions in the electronic search for trials. We last searched the electronic databases on 22 May 2018.

Selection criteria

We planned to include randomized controlled trials (RCTs) comparing at least two of the following interventions with each other for the treatment of orbital lymphangiomas: observation; sildenafil therapy; sirolimus therapy; sclerotherapy; surgery (partial or complete resection). We planned to include trials that enrolled children and adults up to 32 years of age, based on a prior clinical trial protocol. There were no restrictions regarding location or demographic factors.

Data collection and analysis

Two review authors independently screened the titles, abstracts, and full articles to assess their suitability for inclusion in this review. No risk of bias or data extraction was performed because we did not find any trials for inclusion. If there had been RCTs, two authors would have assessed the risk of bias and abstracted data independently with discrepancies being settled by consensus or consultation with a third review author.

Main results

There were no RCTs that compared any two of the mentioned interventions (medical or surgical) for treating orbital lymphangiomas in children and young adults.

Authors' conclusions

Currently, there are no published RCTs of orbital lymphangioma treatments. Without these types of studies, conclusions cannot be drawn regarding the effectiveness of the medical and surgical treatment options for patients with orbital lymphangiomas. The presence of only case reports and case series on orbital lymphangiomas makes it clear that RCTs are needed to address the differences between these options and help guide treatment plans. Such trials would ideally compare outcomes between individuals randomized to one of the following treatment options: observation, sclerotherapy, systemic sirolimus therapy, systemic sildenafil therapy, and surgical excision.

PLAIN LANGUAGE SUMMARY

Interventions for orbital lymphangioma

What is the aim of this review?
We planned this Cochrane Review to analyze the effectiveness, recurrence rate, and side effects of the four major interventions used to treat orbital lymphangiomas including: observation (watching without intervention until the lymphangioma caused problems such as a decrease in vision or inability to close the eye); sclerotherapy (injections into the lesion that scar the lesion into a smaller size); medications taken by mouth; and surgery. The goal was to establish the relative effectiveness of treatment as measured by symptom improvement (such as droopy eyelid or swelling), decreasing lesion size, and quality of life improvement.

Key messages
Currently, there are no eligible randomized controlled trials (RCTs) comparing treatment options for orbital lymphangioma. Therefore, the effectiveness, recurrence rate, and side effects of the four major interventions used to treat orbital lymphangiomas remains uncertain.

What was studied in this review?
Lymphangiomas are localized malformations of the vascular and lymphatic system that most commonly occur in the head and neck regions of children. Lymphangiomas of the orbit (eye socket) typically present in children under the age of 16 years old with ptosis (droopy eyelid), swelling around the eye area, or with bleeding within the lesion from a minor injury. People with this condition can also present with other symptoms such as cosmetic deformity, proptosis (protrusion of the eye), restriction of eye movement (an eye that looks like it is wandering and can lead to vision loss in a child), compression of the optic nerve (a type of vision loss), and amblyopia (another type of vision loss) in children. Due to these vision-threatening complications, early and effective treatment is crucial in preventing cosmetic disfigurement, pain, and visual impairment.

Orbital lymphangiomas are notorious for being very difficult to treat due to how close they are to the eye and other important structures of the eye socket, all of which are needed for good vision. Treatment type also depends on lymphangioma size, cyst type, and location. One option is called observation, and this means carefully watching patients without doing any treatment. This is because some tumors are smaller or in hard-to-reach locations and are not threatening the vision. This may be a good option since each treatment option has side effect risks. For example, surgery can damage nearby structures, while medications by mouth can cause fever, diarrhea, headaches, and high blood pressure, amongst other problems. The option of surgery has typically been delayed until absolutely necessary as there is a high rate of the lesion growing back, there is a high risk to surrounding tissue (like the eye, the optic nerve, the eye muscles), and it is difficult to remove the entire lesion. In addition to observation and surgery, another treatment option is to inject agents called sclerosants into the lesions with the goal of reducing their size. Finally, in lesions that are difficult to access surgically or with injections, medication taken by mouth (called 'systemic medication') has also been used to reduce the size and resulting symptoms. The goal of these therapies is to reduce cosmetic disfigurement and pain caused by these lesions, in addition to avoiding vision-threatening complications.

What are the main results of the review?
A search of the current literature and research on this topic yielded 5258 journal articles but no RCTs comparing two types of orbital lymphangioma treatments were found. Therefore no conclusions can be drawn about the effectiveness of the four major interventions of interest in treating people with orbital lymphangioma. It is clear from this review that further studies are needed that randomize people into these various treatments. Of note: there is one ongoing study that may meet these criteria, which is expected to be completed in 2021.

How up to date is this review?
The review authors searched for studies that had been published up to 22 May 2018.

BACKGROUND

Description of the condition

Lymphangiomas are localized, multi-cystic malformations of the lymphatic and vascular systems, most commonly occurring in the head and neck region of children. The prevalence of lymphangiomas has been estimated to be 1.1 to 5.3 cases per 10,000 live births, although population-based studies including live births along with terminated pregnancies and stillbirths estimate the prevalence to be 30 cases per 10,000 (Forrester 2004). Lymphangiomas represent 4% of all vascular tumors and approximately 25% of all benign pediatric vascular tumors (Grasso 2008). Lymphangiomas involving the orbit constitute around 1% to 4% of all orbital lesions (Nassiri 2015). In a 30-year retrospective study of 1254 patients presenting to an ocular oncology service, Shields and colleagues found that orbital lymphangiomas accounted for 25% of all orbital vascular lesions and 4% of the total number of orbital lesions (Shields 2004). The rarity of orbital lymphangiomas contributes to the difficulty in determining universal treatment guidelines.

The most frequent presenting features of orbital lymphangiomas are ptosis and proptosis with the majority of orbital lymphangiomas presenting in the first decade of life. Studies have shown that 43% of cases are diagnosed before the age of 6 years old and 60% are diagnosed before the age of 16 years, with equal distribution between males and females (Nassiri 2015). Diagnosis tends to occur earlier for more superficial lesions and later in life for deeper lesions. The lesions can enlarge with systemic infections, typically during an upper respiratory infection or with minor trauma, which results in intralesional hemorrhage (Kalisa 2001; Raichura 2017). Other presentations can include extraocular motility restriction, physical disfigurement, mechanical blepharoptosis (which can obstruct visual development and result in amblyopia), and compressive optic neuropathy (Saha 2012). Early and effective treatment, especially in children, is therefore crucial to preserving vision and preventing amblyopia.

Management of orbital lymphangiomas depends heavily on understanding anatomic makeup. Orbital lymphangiomas are classified as “type 1: no flow” lesions, as per the International Orbital Society vascular malformation classification system (type 1 [no flow], type 2 [venous flow], type 3 [arterial flow] lesions). Orbital lymphangiomas have minimal internal blood flow and little to no connection with the vascular system (Harris 1999). This allows for the use of sclerosant therapy, as opposed to vascular malformations with high flow or prominent connections to the vascular system, or both.

Another important mode of classification is based on vascular lesion type, since many malformations are not just one type of vascular malformation. For example, a lesion could be made of venous and lymphatic components and the classification would be based on which entity is the most predominant (i.e. 'lymphatic dominant' vs 'venous dominant'). These distinctions can potentially predict which treatments are more effective, as seen in a study showing lymphangiomas with a venous component may respond better to oral sirolimus (Adams 2016).

Finally, management is also dependent on depth of involvement and cyst size. More specifically, the depth categories are:

- superficial (presenting as a subcutaneous cyst);
- deep (orbital infiltration);
- combined (superficial and deep components);
- complex (intracranial or head and neck infiltration) (Saha 2012).

Malformations that are superficial are easier to target with sclerotherapy and surgery, while deep, combined, or complex malformations may present more risks if a procedural approach is attempted. Cyst size also directs practicality and effectiveness of treatment. For example, there are microcysts, macrocysts (> 2 cm in size), and mixed cysts (Hill 2012), but typically only macrocysts are considered for sclerotherapy (Bagrodia 2015; Hanif 2018).

Lymphangioma diagnosis is best confirmed with radiologic imaging to concurrently assess size and extent. Classically, they are characterized by multiple cysts with pathognomonic fluid levels. They are isointense on T1-weighted magnetic resonance imaging and hyperintense on T2-weighted imaging, presenting with internal septations. As lymphangioma are classified as 'no flow' lesions, there is typically an absence of flow voids and enlarged feeder vessels (Raichura 2017).

The non-encapsulated and infiltrative nature of lymphangiomas mean that they surround vital structures of the orbit, leading to the high risk of morbidity and recurrence with many interventional treatment modalities (Bloom 2004; Raichura 2017).

Description of the intervention

With the lack of one clear effective therapy for orbital lymphangiomas and the proximity to vital structures, such as the globe, optic nerve, and extraocular muscles, treatment for orbital lymphangiomas is complicated and includes a large array of approaches. The major interventions fall into four categories: observation (if the lesion is not causing pain, physically disfiguring, or vision threatening); intralesional sclerosant injections; systemic medication; and surgery.

Observation

Observation can be considered for patients in whom vision is not threatened and there are no significant symptoms. As complete excision is difficult with high risk of morbidity and recurrence, there are many patients and physicians who opt to monitor until any of the following occur: amblyopia; compressive optic neuropathy; exposure keratopathy; and severe cosmetic disfigurement (Bloom 2004; Saha 2012).

Sclerotherapy

Sclerosants have been used for the treatment of orbital lymphangiomas for the past three decades. Specific agents include OK-432 (Picibanil), sodium tetradecyl sulfate, doxycycline, ethanol, pingyangmycin, and bleomycin (Gandhi 2013). These agents are administered under ultrasound guidance by puncturing the cystic cavity, aspirating the fluid, and injecting the sclerosing agent. By aspirating the fluid, a diagnosis of the lesion can be confirmed by cytology and the surface area in contact with the agent is increased. It is important to note that sclerotherapy has been reported to be effective in treating and resolving macrocystic lymphatic malformations, with less efficacy seen in their microcystic counterparts (Bagrodia 2015). Sclerotherapy comes with risks, such as infection, bleeding, risks of damage to adjacent structures, increased orbital pressure due to the

volume of injecting fluid, hemorrhage, and post-injection reactive inflammation (Raichura 2017). Increased orbital pressure can result in decreased blood supply to the optic nerve and permanent vision loss.

Systemic sildenafil

Systemic sildenafil therapy is a novel approach to treating lymphatic malformations that has shown positive results in both orbital and non-orbital lymphatic lesions. It is a phosphodiesterase 5 (PDE-5) inhibitor, which increases the levels of cyclic guanosine monophosphate in smooth muscles, leading to vasodilatory effects (Gandhi 2013). Already in use in the pediatric population for pulmonary arterial hypertension, a low dose of oral sildenafil citrate has been shown to be a safe and effective method of decreasing the volume of lymphatic malformations in some children, especially those whose lesions are characterized as macrocystic or mixed (Wang 2017). Malformations have been shown to be reduced using a dose of 1 mg/kg/day of sildenafil and increasing the dose to 3 mg/kg/day, with longer-term use (seven months) (Gandhi 2013; Wang 2017). To date, no adverse events have been described (Gandhi 2013).

Systemic sirolimus

Sirolimus is another novel therapy for orbital lymphatic malformations. It is a target of rapamycin (mTOR), which stops the integration of signals from the PI3K/AKT pathway to coordinate proper cell growth and proliferation by regulating ribosomal biogenesis and protein synthesis. The blocking of this pathway leads to a reduction in vascular endothelial growth factor production and angiogenesis, along with a reduction in the production of cytokine IL-2. In certain cases, sirolimus has been shown to be effective based on both radiologic evaluations and functional impairment scores. Adams and colleagues showed that sirolimus had a particularly strong response for arterial venous malformations and venous lymphatic malformations (Adams 2016). Dosing is typically 0.8 mg/m^2, with optimal serum trough levels of 10 ng/mL to 15 ng/mL. Monitoring is required with serum trough levels typically taken every five to seven days after initiation of treatment (Adams 2016). Systemic sirolimus does come with side effects, some of which are serious enough to limit its use in certain patients. These side effects include persistent nausea, peripheral edema, hypertriglyceridemia, fever, cold symptoms, stomach pain, and diarrhea (Adams 2016).

Surgical excision and debulking

Another intervention for orbital lymphangiomas is surgical debulking. However, since lymphangiomas tend to intertwine with vital orbital structures, debulking or complete excision can damage adjacent structures (Saha 2012). In addition to risk of damage to adjacent structures, surgery comes with a significant risk of recurrence and scarring (Patel 2017). To aid with hemostasis and surgical manipulation, surgery can be accompanied with sclerotherapy or other intralesional therapy, such as fibrin glue. Fibrin glue injected intraoperatively into the lesion allows the surgeon to have improved hemostasis and a more solid mass to mobilize and successfully excise. In severe cases, when there is an orbital lymphangioma in the posterior orbit with a blind and painful eye, orbital exenteration can be considered (Saha 2012).

How the intervention might work

Due to the complicated nature of orbital lymphangiomas, the interventions described focus on reducing size and progression with the goal of eliminating pain, proptosis, amblyopia, hemorrhage, and optic neuropathy. The mechanism of action for each of these treatments is unique to the treatment.

The mechanism of action of sclerotherapy depends on the type of medication, Sclerotherapy is an umbrella term for multiple types of medications which are injected into each cyst within the lesion, causing scarring to reduce the size of the targeted cyst (Patel 2017). These sclerosants are classified into three types of mechanisms of action. One mechanism of action is to enhance endothelial cell death, as seen in sodium tetradecyl sulfate, ethanol, and doxycycline. Another mechanism of action by chemotherapeutic agents (like bleomycin and pingyangmycin) inhibits cell proliferation and promotes inflammatory responses that lead to cell death. Finally there are compounds, like OK-432 for example, that promote inflammatory responses that lead to cytokine production from circulating lymphocytes. These cytokines act on the endothelium of the lymphangioma, increasing the permeability, leading to faster lymph flow and drainage and resulting shrinkage of the cystic space (Suzuki 2000).

Another lymphangioma treatment is sildenafil, which is taken orally by the patient. Systemic sildenafil therapy reduces the size of the lesion by inhibiting PDE-5, which is a smooth muscle relaxant. Since the cysts of lymphangiomas are thought to dilate from contraction of the muscular lining of vascular channels, sildenafil therapy is believed to reduce the size of the lesion by relaxing the smooth muscle of these vascular channels, leading to a reduction in lesion size (Gandhi 2013).

Another oral treatment for lymphangioma is sirolimus. Systemic sirolimus therapy reduces the size of the lesion through reduction in angiogenesis and cell growth. Sirolimus is a target of mTOR, leading to a disruption in the P13K/AKT pathway. Normally this pathway governs cell growth, leading to lymphangiogenesis and angiogenesis. Disorders in this pathway lead to abnormal tissue overgrowth and result in vascular anomalies (Adams 2016). In lymphangiomas, sirolimus is therefore intended to disrupt this pathway, reducing angiogenesis and cell growth, and ultimately leading to a reduction in the lesion size.

The final treatment option in discussion is surgical debulking. Since complete surgical excision is often unsuccessful due to the intertwining nature of lymphangioma, debulking is done with the primary goal of preventing vision loss or improving cosmesis. This can be combined with non-surgical interventions; or intraoperative fibrin glue or sclerosing agents; or both (Saha 2012).

Why it is important to do this review

Orbital lymphangiomas can lead to severe visual, cosmetic, and quality-of-life issues for patients. There is no consensus on the best first-line intervention to treat this condition. Surgical resection is a challenge due to the lesion's unencapsulated nature and proximity to vital orbital structures. The difficulty and danger of excision is paired with a high recurrence rate of the lesions which can occur up to many years after initial surgery (Russin 2015).

When considering alternative treatments, sclerotherapy and systemic sildenafil and sirolimus are viewed as less invasive

methods to reduce lesion size. A review article that compared surgical debulking/excision to primary sclerotherapy for the treatment of head and neck lymphatic malformations suggested no difference in effectiveness one year post intervention (Bagrodia 2015). No such study exists for sildenafil and sirolimus. While the Bagrodia 2015 study suggests non-inferiority of sclerosants in head and neck lymphangiomas, this was not a randomized controlled study. There continues to be a lack of clinical consensus on the most effective treatment option.

In this review, the aim was to examine current literature regarding each of these treatments and analyze the effectiveness, recurrence rate, and side effects of each.

OBJECTIVES

To assess the effectiveness of medical and surgical interventions for the reduction/treatment of orbital lymphangiomas in children and young adults.

METHODS

Criteria for considering studies for this review

Types of studies

We only considered randomized controlled trials (RCTs) for this review. There were no date or language restrictions.

Types of participants

We planned to include patients if they participated in an RCT comparing at least two orbital lymphangioma managements. Patients were to be of age 32 years and below, based on the typical onset in childhood (NCT00975819). There were no restrictions regarding location or demographic factors.

Types of interventions

RCTs comparing at least two of the following interventions with each other for the treatment of orbital lymphangiomas.

- Observation.
- Sildenafil therapy.
- Sirolimus therapy.
- Sclerotherapy.
- Surgery (excision or debulking).

The primary comparison of the review was surgical versus non-surgical (sclerotherapy, sildenafil, sirolimus, or observation) therapy. Secondary comparisons included sclerotherapy versus systemic therapy (sildenafil or sirolimus) and sclerotherapy versus observation.

Types of outcome measures

Primary outcomes

The primary outcome was reduction in lymphangioma size up to two years after intervention based on clinical assessment or imaging, or both.

Secondary outcomes

- Levels of pain post therapy (as reported by participants) up to two years after the intervention. We planned to analyze patient-reported pain as both continuous or non-continuous. Continuous pain measures included mean level of pain or mean change in pain, whereas non-continuous pain measures would be analyzed as improvement, no change, and worsening.
- Functional impairment related to ptosis and exposure keratopathy up to two years after the intervention. We defined functional impairment as the inability to perform daily activities (as reported by participants) due to the ptosis or exposure keratopathy. Functional impairment could be reported as continuous (mean or mean change) or non-continuous (improvement, no change, or worsening) measures.

Adverse effects

We planned to document and quantify any adverse effect reported in the included studies related to systemic therapy or surgery. Specific adverse effects of interest in this review included recurrence or increased size of the mass after surgery, infections following treatment, damage to surrounding orbital structures during surgery or sclerosant injection or both, increased pain, increased eyelid edema, increased pressure in the orbit due to volume of injections, and any systemic adverse effects.

Economic data

We did not plan to evaluate economic data.

Quality of life data

We planned to analyze quality of life scores (mean or mean change) obtained with a validated questionnaire whenever this information was available. These scores could include patient/caregiver's satisfaction with the treatment and satisfaction with any associated cosmetic and functional changes.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for randomized controlled trials and controlled clinical trials. There were no restrictions on language or publication year. The electronic databases were last searched on 22 May 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 5) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 22 May 2018) (Appendix 1).
- MEDLINE Ovid (1946 to 22 May 2018) (Appendix 2).
- Embase.com (1947 to 22 May 2018) (Appendix 3).
- PubMed (1948 to 22 May 2018) (Appendix 4).
- Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 22 May 2018) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 22 May 2018) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 22 May 2018) (Appendix 7).

Searching other resources

We planned to search the reference lists of trials included in this review for additional trials of interest, in addition to the Science Citation Index, in order to find trials that cited the identified trials.

Data collection and analysis

Selection of studies

Two review authors independently reviewed the abstracts and titles of articles identified through the electronic searches, using the criteria for considering studies for this review, and classified the titles and abstracts into three categories: 'definitely use,' 'possibly use,' and 'definitely exclude.' Any disagreements on classification were resolved through discussion between the two review authors. After all review authors were in agreement, the full-text reports of studies classified as 'definitely use' and 'possibly use' were retrieved. Each review author independently assessed these reports for the inclusion criteria and classified them as 'include,' 'unsure,' and 'exclude.' We resolved any disagreements regarding study selection through discussion, and documented reasons for exclusion. All studies that met inclusion criteria would have undergone assessment of risk of bias and data extraction.

During the selection process, no trials were eligible for inclusion in this review. The methods described below will be applicable to future updates of the review when trials eligible for inclusion have been conducted and reported.

Data extraction and management

We planned to have two review authors independently extract data regarding study design, participant characteristics, and interventions and outcomes assessed, using the data extraction forms developed by Cochrane Eyes and Vision (Appendix 8). The review authors were to discuss discrepancies. If any issue were to arise with a specific study, study investigators were to contact study authors to request clarification regarding methods or missing information. One review author was to enter data into Review Manager 5 (RevMan 5) (Review Manager 2014); and a second review author was to verify the data.

Assessment of risk of bias in included studies

We planned to follow the guidelines provided in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias in included studies (Higgins 2017). We would have considered the following domains.

- Random sequence generation (selection bias).
- Allocation concealment; prior to randomization (selection bias).
- Masking (blinding) of participants and personnel (performance bias).
- Masking (blinding) of outcome assessors (detection bias).
- Incomplete outcome data (attrition bias).
- Selective outcome reporting (reporting bias).
- Other sources of bias.

We planned for two review authors to independently conduct bias assessment. We would have categorized each study for each potential source of bias as at 'high', 'low', or 'unclear' risk of bias. We would have resolved any disagreements by discussion. We would have contacted study investigators when methods were reported unclearly or incompletely.

Measures of treatment effect

We would have categorized outcomes as either continuous or non-continuous. For continuous outcomes, such as reduction in lymphangioma size and changes in quality of life scores, we would have calculated mean differences (MDs) and 95% confidence intervals (95% CIs) to estimate treatment effects. For non-continuous outcomes, such as the proportion of participants with adverse effects, we would have calculated risk ratios (RRs) with 95% CIs to estimate treatment effects. We would have reported secondary outcomes of patient-reported pain and functional impairment as continuous (mean or mean change) or non-continuous (proportions with improvement, no change, or worsening) measures.

Unit of analysis issues

The primary unit of analysis was to be one eye per participant, with the unit of analysis being the participant. For any trials that included both eyes, assessment would be required to decide if appropriate analysis was used for correlated outcomes in pairs of eyes. We planned to document the study design with respect to the treatment modality and treatment of either one or both eyes, and how the correlation was handled.

Dealing with missing data

In order to elucidate study reports missing outcome data, unclear study methods, outcome data, or any other information that could hinder our classification of the study for inclusion or exclusion in our review, the plan was to contact study authors. This was to be done via email with two weeks allowed for a response with the requested information. If we could not retrieve the missing information for an included study, we would then have classified the study as missing data when discussing the results.

Assessment of heterogeneity

In order to assess clinical and methodological heterogeneity, we planned to compare inclusion/exclusion criteria of included trials, characteristics of study participants, and assessments of primary and secondary outcomes. We planned to use the I^2 statistic (percentage) to judge statistical heterogeneity among studies included in any meta-analysis. This statistic estimates the proportion of variation in outcome estimates due to statistical heterogeneity that cannot be attributed to random error. We would have considered an I^2 value over 50% to indicate substantial statistical heterogeneity (Deeks 2017). The plan was to generate forest plots and assess them for consistency of direction and size of the effect among studies. The plan was to consider the degree of overlap in CIs among individual studies, with poor overlap of CIs indicating the presence of heterogeneity.

Assessment of reporting biases

In order to assess reporting bias, we planned to compare outcomes reported in each included trial to the outcomes listed in the original study protocol, design report, or registry record to judge whether selective outcome reporting was likely. If a sufficient number of studies (more than 10) were included in our review for individual outcomes, the plan was to examine funnel plots for evidence of asymmetry, which may imply possible publication bias.

Data synthesis

After considering the assessment of heterogeneity and the number of included trials, the plan was to perform a meta-analysis for each outcome using either a random-effects or fixed-effect model. If substantial clinical or methodological heterogeneity was observed, according to the criteria detailed above, we would not have combined outcome data from individual trials in a meta-analysis, but would, instead, have presented findings in a narrative description. When there was no evidence of clinical, statistical, or methodological heterogeneity and three or more trials were included in a meta-analysis, our plan was to use a random-effects model. When there was no evidence of clinical, statistical, or methodological heterogeneity and fewer than three trials were included in a meta-analysis, our plan was to use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We did not plan to conduct any subgroup analysis.

Sensitivity analysis

When sufficient data was available, our plan was to conduct sensitivity analysis to evaluate the effects of excluding studies deemed as at overall high risk of bias. We planned to report these findings in a tabular format.

Summary of findings

We planned to summarize findings in a table with respect to estimates of primary and secondary outcomes and adverse effects of treatments. Additionally, we planned to summarize the strengths and limitations of both primary and secondary outcome estimates. We would have assessed the certainty of the evidence to support each estimate using the GRADE approach (GRADEpro 2015).

We planned to report the following outcomes in 'Summary of findings' tables.

- Reduction in lymphangioma size (assessed up to a period of two years after the intervention).
- Self-reported pain (post-therapy, assessed up to a period of two years after the intervention).
- Functional impairment related to ptosis and exposure keratopathy (assessed up to two years after the intervention).
- Quality of life (assessed up to two years after the intervention).
- Adverse effects (assessed up to two years after the intervention).

Potential pair-wise comparisons included:

- surgical excision/debulking versus observation;
- surgical excision/debulking versus sildenafil;
- surgical excision/debulking versus sirolimus;
- surgical excision/debulking versus sclerotherapy;
- sildenafil therapy versus observation;
- sildenafil therapy versus sirolimus;
- sildenafil therapy versus sclerotherapy;
- sirolimus therapy versus observation;
- sirolimus therapy versus sclerotherapy;
- sclerotherapy versus observation.

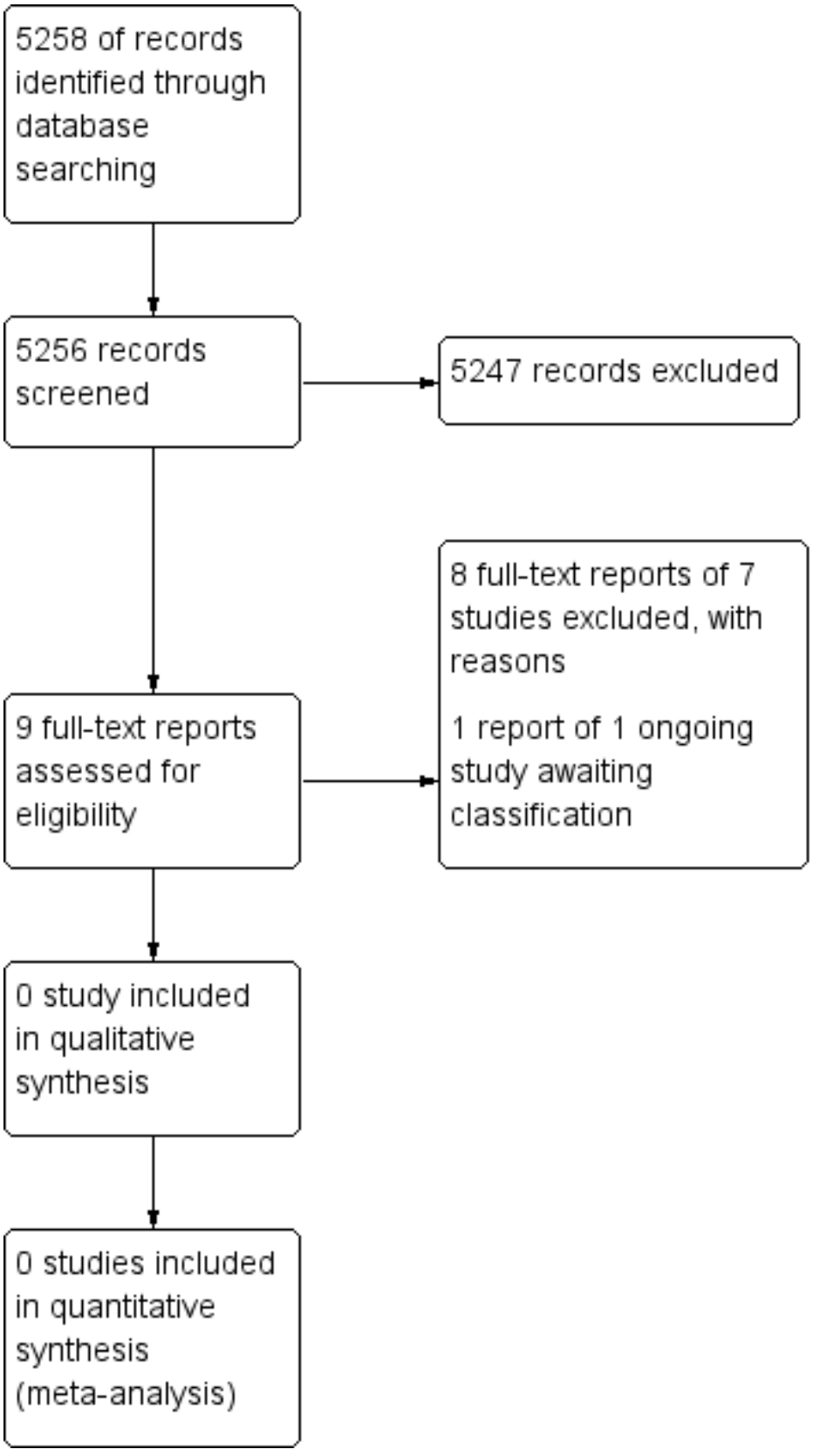
RESULTS

Description of studies

Results of the search

From the electronic searches, we retrieved 5258 references to studies in May 2018 (Figure 1). Of these 5258, we removed two duplicates. After examination of the titles with abstracts of these references, we excluded 5247 reports which did not match inclusion criteria or were otherwise ineligible. After exclusion, we obtained full-text reports of the remaining nine potentially eligible reports for deeper evaluation. The review authors discussed the eligibility of these trials and resolved any disparities in opinion by consensus. We excluded eight reports of seven studies from the review, with reasons documented below. We identified one ongoing study Stanford 2022, which will be assessed for potential inclusion in the review when data becomes available.

Figure 1. Study flow diagram.



Included studies

No studies were eligible for inclusion in this review.

Excluded studies

We excluded seven studies: four were not RCTs (Barnacle 2016; Muallem 2000; Sires 2001; Swetman 2012); two were not RCTs, with in addition a study population which did not include any patients with orbital lymphangiomas (Şanlialp 2003; Şanlialp 2004); and one RCT was excluded as it did not include any patients with orbital lymphangiomas (Smith 2009). One study was classified as an ongoing RCT (Stanford 2022).

Risk of bias in included studies

No trials were eligible for inclusion in this review; therefore, risk of bias was not assessed.

Allocation

No trials were eligible for inclusion in this review; therefore, risk of bias was not assessed.

Blinding

No trials were eligible for inclusion in this review; therefore, risk of bias was not assessed.

Incomplete outcome data

No trials were eligible for inclusion in this review; therefore, risk of bias was not assessed.

Selective reporting

No trials were eligible for inclusion in this review; therefore, risk of bias was not assessed.

Other potential sources of bias

No trials were eligible for inclusion in this review; therefore, other potential sources of bias was not assessed.

Effects of interventions

No studies were eligible for inclusion in this review; therefore, effects of interventions were not assessed.

DISCUSSION

Orbital lymphangiomas, although benign, can progress to causing pain, severe globe displacement, cosmetic disfigurement, and problems with visual development and acuity in children (Bagrodia 2015; Honavar 2017). Orbital lymphangiomas are difficult to treat effectively and these lesions have been observed as long as possible because surgical resection is difficult with an increased risk of recurrence and damage to adjacent structures (Patel 2017; Saha 2012). More recently, other treatment options such as intralesional sclerotherapy and systemic sildenafil or sirolimus therapy have been used with varying levels of success. There is no current consensus on the first-line treatment for orbital lymphangiomas. A literature review from 2015 recommended that patients presenting with orbital lymphangioma should be observed first with the option of sclerotherapy for symptomatic macrocysts and surgical debulking for patients with life-threatening disease or microcysts (Bagrodia 2015). Bagrodia and colleagues also mentioned findings regarding the efficacy of oral agents such as sildenafil and sirolimus; however the authors did not give any clinical practice recommendations due to the lack of randomized controlled trials on these agents. This Cochrane Review revealed that no RCTs met inclusion criteria; and that there is therefore a need for future RCTs to compare orbital lymphangioma treatments.

Summary of main results

In this review, an extensive search of electronic literature databases was conducted in order to identify RCTs that evaluated the effectiveness of various medical and surgical treatment options in the management of orbital lymphangiomas. Even with this sensitive search strategy, which included over 5000 results, no RCTs met the inclusion criteria. This search highlights the need for prospective, randomized studies examining effectiveness of medical and surgical treatments for orbital lymphangiomas.

Overall completeness and applicability of evidence

Detailed below in 'Agreements and disagreements with other studies or reviews' section.

Quality of the evidence

Detailed below in 'Agreements and disagreements with other studies or reviews' section and 'Authors' conclusions' section.

Potential biases in the review process

In order to minimize any potential biases that may have arisen during the review process, the highly sensitive search for trials followed the rigorous methods and procedures as recommended by the Cochrane Eyes and Vision group. All non-randomized studies were not included due to the high risk of bias.

Agreements and disagreements with other studies or reviews

To date, the only reviews that evaluate the effectiveness of the various medical and surgical treatment options for orbital lymphangiomas were not based on RCT evidence. The majority of evidence is low tiered: case reports, case series, retrospective studies, and interventional case series. As no RCTs have been conducted, the best evidence present today regarding the effectiveness of the various management options is of low quality, of which only two involve the orbit.

One of these interventional case series was a prospective study of 29 patients with orbital lymphangioma (Barnacle 2016). All of the patients in this trial had macrocystic lymphatic malformations of the orbit and underwent sclerotherapy injection with sodium tetradecyl sulfate with an average follow-up of 21.8 months. All patients achieved improvements in this review's primary endpoints: a reduction in maximal lesion diameter of 50% or more, with complete radiological resolution in 51.7% (n = 15), and improvement from baseline visual acuity in 78.2% of patients. Of note: the adverse event rate was 14% (n = 1), with a patient requiring a lateral canthotomy for an intralesional hematoma that occurred 2 hours after injection. The other interventional case series examined efficacy of sclerotherapy with bleomycin injections in 13 patients with orbital lymphangiomas (Raichura 2017). With a mean follow-up of 19.69 months, there was a more than 60% reduction in maximal diameter of the lesion on MRI in 92% (n = 12) of the patients with no adverse events reported.

These two prospective interventional studies unfortunately represent the current clinical evidence for treatment in orbital lymphangioma, but they only examine sclerotherapy. The evidence for sildenafil and sirolimus for orbital lymphangioma is based on case series only. While there are several studies on sildenafil for lymphangiomas of the neck, there are only two on sildenafil for orbital lymphangiomas specifically. One is a prospective pilot study that documented the effect of a 12-week trial of sildenafil in two children with disabling lymphatic malformations, with one of these patients having a malformation involving the orbit (Swetman 2012). The malformation in one patient was initially debulked due to risk of amblyopia and subsequently treated with sildenafil. The authors noted that within 3 weeks of treatment with sildenafil, the patient had improved opening of the affected eye (Swetman 2012). The other study looking at oral sildenafil in orbital lymphangioma was a retrospective case series of two patients (Gandhi 2013). This study noted significant reductions in the sizes of orbital lymphangiomas on oral sildenafil therapy with reduction of cheek and orbital swelling (allowing patching therapy for amblyopia) in one patient and reduction of facial swelling, lid swelling, and pain in the second patient (Gandhi 2013). Of note: sildenafil has a benign side effect profile and no adverse events were observed.

The level of evidence is similarly limited for oral sirolimus for orbital lymphangioma. There are studies showing effectivity of sirolimus in lymphangiomas in general, but only one case report of orbital lymphangioma specifically. Lagreze 2018 reported a case of a 23-year-old man, who presented with a retrobulbar microcystic lymphangioma in the right orbit that resulted in an 11 mm exophthalmos. Due to the microcystic nature of the lesion, the patient was started on oral sirolimus at 1 mg twice a day, with blood levels maintained between 5 ng/mL to 10 ng/mL for 6 months. After treatment, the lesion had clinically and radiographically regressed to an exophthalmos of 2 mm (Lagreze 2018). Other studies, such as the one conducted by Adams 2016, showed partial clinical and radiologic improvements of vascular anomalies of the head and neck in children after treatment with an oral sirolimus dose of 0.8 mg twice a day for 12 courses (one course was 28 days). However, this study was not specific to orbital lymphangiomas.

Finally, the studies available on surgical excision of orbital lymphangiomas are also limited to a few case series. Russin 2015 assessed eight patients diagnosed with orbital lymphangioma, who underwent surgical resection of their lesions. Presenting symptoms of patients included headache, retro-ocular pain, restriction of eye movement, diplopia, blurry vision, and proptosis. Six of the seven patients who were followed up experienced improvements in their presenting symptoms at a mean of 5.3 years. However, recurrence was seen in 5/7 (71%) of patients at a mean of 7.2 years after the initial procedure. Post-operatively, 37.5% of patients (n = 3) had new or worsened cranial nerve defects, which resolved at the last follow-up assessment.

A second study on surgical excision of orbital lymphangiomas was a retrospective case of five patients by Simas 2014. Pre-operatively, all five patients had proptosis with two of the five experiencing visual acuity deficits. Computed tomography and magnetic resonance imaging showed multilobulated infiltrative lesions that occupied intra- and extraconal spaces. All patients underwent subtotal resection of the lesion with a pterional, lateral, or anterior superomedial approach. At a median follow up of 3.2 years, all patients had recovered from proptosis, with improvement in visual acuity in those who had presented with decreased visual acuity. During the follow-up period, no patients presented with a recurrence of their tumor or any hemorrhagic episodes (Simas 2014). Berthout and colleagues showed similar findings in a case series of two patients who underwent subtotal resection of orbital lymphangiomas with improvements in proptosis and no recurrence of hemorrhage and tumor growth at a follow-up time of 12 months (Berthout 2008).

In addition to these studies on surgical excision for orbital lymphangioma, there are two other reports of surgical excision in conjunction with fibrin glue. Hayasaki 2009 reported a case of a 2-year-old girl presenting with exophthalmos and upper lid swelling, who was found to have a multilobular orbital lymphangioma. She underwent a frontal craniotomy and the cyst was punctured and drained with partial resection of the cyst wall. However, a week later, the lesion had regrown, so a secondary resection was performed with intraoperative, intralesional injection of tissue fibrin glue. After follow-up of a few weeks, there were no signs of recurrence of the lesion in the orbit and her clinical symptoms had complete resolution (Hayasaki 2009). Similar results were reported in a case series of three patients who underwent surgical resection of their lymphangiomas with intralesional injection of fibrin sealant, with all cases showing improvement in their symptoms with no follow-up complications (Boulos 2005).

Of note: there is currently an ongoing double-blind placebo-controlled trial assessing the effectiveness of placebo versus oral sildenafil (20 mg) in the treatment of orbital lymphangiomas (Stanford 2022). In this study, the investigators are assessing 40 participants, aged 6 months to 10 years old, with lymphatic malformations greater than 3 cm, confirmed by magnetic resonance imaging. Their primary outcome of interest includes a change in lesion volume within 20 weeks of treatment with the oral medication.

While there are a number of case series and reviews, there are no published prospective RCTs comparing effectiveness and side effects of orbital lymphangioma treatments.

AUTHORS' CONCLUSIONS

Implications for practice

This comprehensive examination of the literature is the first systematic review of orbital lymphangioma treatments. It exposes the lack of RCTs evaluating the effectiveness of medical and surgical treatment options for orbital lymphangioma. While the relatively low prevalence of orbital lymphangiomas and the incredibly varied presentations pose challenges to orchestrating an effective trial, developing future RCTs with the collaboration of multiple institutions will be important in creating an evidence-based treatment paradigm.

Based on the existing evidence and clinical practices, the most common management is to observe orbital lymphangiomas until there is a decrease in vision (whether directly or due to amblyopia), exposure keratopathy, or severe disfigurement (Bagrodia 2015; Honavar 2017; Lally 2016). Then, treatment depends on size of the cysts, location, and vascular makeup. For cysts 2 cm or larger, which can be accessed via needle, sclerotherapy can be considered (Barnacle 2016; Lally 2016; Patel 2017; Raichura 2017). Oral sildenafil and oral sirolimus are also potentially effective

treatment options, with sirolimus showing better results for those malformations with a venous component (Adams 2016; Gandhi 2013; Lagreze 2018; Russin 2015; Swetman 2012). Surgical excision, with or without the aid of fibrin glue, is also a treatment option with the understanding that complete excision is unlikely.

Implications for research

This systematic review demonstrates the dearth of high-level evidence in determining effectiveness of medical and surgical treatment options for orbital lymphangiomas.

Future trials could apply a cross-over design in which participants are randomized into treatment and non-treatment groups, where patients can then switch to the treatment group after a certain amount of time (Smith 2009; Stanford 2022). In these studies, outcomes measured would include reduction in radiographic size, pain levels, functional impairment due to ptosis, quality of life, ability to perform daily activities, and side effects. This method of study design would allow the measurement of the intervention treatment effect while also delivering treatment to all the patients involved in the study. Due to the rarity of this condition, its varied anatomic involvement, and its mostly pediatric patient population, RCTs may be difficult to conduct. As noted (in Agreements and disagreements with other studies or reviews,) there is currently one such RCT ongoing studying sildenafil versus placebo in pediatric lymphangiomas, including the orbit. This study provides effective study design ideas for those creating an RCT for the other treatment options. Additionally, future studies would ideally include a multi-center approach to recruit larger study populations and would also involve a multi-disciplinary team of pediatric ophthalmologists, interventional radiologists, pediatricians, pathologists, radiologists, and oculoplastic surgeons.

With the breadth of treatment options currently utilized, there is a significant need for well-designed RCTs assessing the effectiveness of each treatment modality in order to best guide treatment plans for patients with orbital lymphangiomas.

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CHARACTERISTICS OF STUDIES

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Study	Reason for exclusion
Barnacle 2016	Not a randomized controlled trial
Muallem 2000	Not a randomized controlled trial
Sires 2001	Not a randomized controlled trial
Smith 2009	Patient population does not meet eligibility criteria
Swetman 2012	Not a randomized controlled trial
Şanlialp 2003	Patient population does not meet eligibility criteria; not a randomized controlled trial
Şanlialp 2004	Patient population does not meet eligibility criteria; not a randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Stanford 2022

Trial name or title	
Methods	Double-masked placebo-controlled trial
Participants	40 participants aged 6 months to 10 years old with lymphatic malformation confirmed on MRI that is greater than 3 cm in diameter.
Interventions	Placebo vs. Oral Sildenafil 20 mg tablets
Outcomes	Primary: Change in lesion volume of the test medication as evaluated by MRI within 20 weeks; Secondary: Change in lesion volume estimated using a soft tape measure to measure the length, width, and hemispheric measurement of each of the lymphatic malformations; Participant's evaluation of the change in lesion clinical characteristics
Starting date	
Contact information	
Notes	

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Orbital Neoplasms] explode all trees
#2 MeSH descriptor: [Eyelid Neoplasms] explode all trees
#3 MeSH descriptor: [Conjunctival Neoplasms] explode all trees
#4 MeSH descriptor: [Lymphatic Abnormalities] explode all trees
#5 MeSH descriptor: [Lymphangioma] explode all trees
#6 lymphangioma* or lymphangioendothelioma*
#7 "cystic hygroma" or "cystic hygromas"
#8 (lymphatic* or lymphic*) near/3 (malformation* or abnormal* or anomal*)
#9 (orbit* or periorbit* or ocular* or oculo* or eyelid* or conjunctiv*) near/3 (lymphatic* or neoplas* or malformation* or tumor*)
#10 {or #1-#9}

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Orbital Neoplasms/
13. exp Eyelid Neoplasms/
14. exp Conjunctival Neoplasms/
15. exp Lymphatic Abnormalities/
16. exp Lymphangioma/
17. (lymphangioma* or lymphangioendothelioma*).tw.
18. cystic hygroma*.tw.
19. ((lymphatic* or lymphic*) adj3 (malformation* or abnormal* or anomal*)).tw.
20. ((orbit* or periorbit* or ocular* or oculo* or eyelid* or conjunctiv*) adj3 (lymphatic* or neoplas* or malformation* or tumor*)).tw.
21. or/12-20
22. 11 and 21

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'orbit tumor'/exp
#34 'eyelid tumor'/exp

#35 'conjunctiva tumor'/exp
#36 'lymphatic malformation'/exp
#37 'lymphangioma'/exp
#38 (lymphangioma* OR lymphangioendothelioma*):ab,ti
#39 "cystic hygroma*":ab,ti
#40 ((lymphatic* OR lymphic*) NEAR/3 (malformation* OR abnormal* OR anomal*)):ab,ti
#41 ((orbit* OR periorbit* OR ocular* OR oculo* OR eyelid* OR conjunctiv*) NEAR/3 (lymphatic* OR neoplas* OR malformation* OR tumor*)):ab,ti
#42 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #32 AND #42

Appendix 4. PubMed search strategy

1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. lymphangioma*[tw] OR lymphangioendothelioma*[tw]
3. cystic hygroma*[tw]
#4 (lymphatic*[tw] OR lymphic*[tw]) AND (malformation*[tw] OR abnormal*[tw] OR anomal*[tw])
#5 (orbit*[tw] OR periorbit*[tw] OR ocular*[tw] OR oculo*[tw] OR eyelid*[tw] OR conjunctiv*[tw]) AND (lymphatic*[tw] OR neoplas*[tw] OR malformation*[tw] OR tumor*[tw])
6. #2 OR #3 OR #4 OR #5
7. #1 AND #6
8. Medline[sb]
9. #7 NOT #8

Appendix 5. LILACS search strategy

(MH:C04.588.149.721.656$ OR MH:C04.588.364.659$ OR MH:C05.116.231.754.659$ OR MH:C11.319.457$ OR MH:C11.675.659$ OR MH:C04.588.443.392.500$ OR MH:C11.319.421$ OR MH:C11.338.526$ OR MH: C04.588.364.235$ OR MH:C11.187.169$ OR MH:C11.319.217$ OR MH: C15.604.451$ OR MH:C16.131.482$ OR MH:C04.557.375.450$ OR lymphangioma$ OR lymphangioendothelioma$ OR "cystic hygroma" OR ((lymphatic$ OR lymphic$) AND (malformation$ OR abnormal$ OR anomal$)) OR ((orbit$ OR periorbit$ OR ocular$ OR oculo $ OR eyelid$ OR conjunctiv$) AND (lymphatic$ OR neoplas$ OR malformation$ OR tumor$))) AND ((PT:"randomized controlled trial" OR PT:"controlled clinical trial" OR PT:"multicenter study" OR MH:"randomized controlled trials as topic" OR MH:"controlled clinical trials as topic" OR MH:"multicenter studies as topic" OR MH:"random allocation" OR MH:"double-blind method" OR MH:"single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro")

Appendix 6. ClinicalTrials.gov search strategy

Lymphangioma OR lymphangioendothelioma OR "cystic hygroma" OR ((orbit OR orbital OR periorbital OR eyelid OR conjunctival) AND (lymphatic OR neoplasm OR malformation OR tumor))

Appendix 7. WHO ICTRP search strategy

Lymphangioma OR lymphangioendothelioma OR cystic hygroma OR orbit AND lymphatic OR orbit AND neoplasm OR orbit AND malformation OR orbit AND tumor OR orbital AND lymphatic OR orbital AND neoplasm OR orbital AND malformation OR orbital AND tumor OR ocular AND lymphatic OR ocular AND neoplasm OR periorbital AND lymphatic OR periorbital AND neoplasm OR periorbital AND malformation OR periorbital AND tumor OR ocular AND lymphatic OR ocular AND neoplasm OR ocular AND malformation OR ocular AND tumor OR eyelid AND lymphatic OR eyelid AND neoplasm OR eyelid AND malformation OR eyelid AND tumor OR conjunctival AND lymphatic OR conjunctival AND neoplasm OR conjunctival AND malformation OR conjunctival AND tumor

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	• **Parallel-group RCT***i.e. people randomized to treatment* • **Within-person RCT***i.e. eyes randomized to treatment* • **Cluster RCT***i.e. communities randomized to treatment*	Exclusions after randomization Losses to follow-up

(Continued)

	• **Cross-over RCT** • Other, specify	Number randomized/analyzed
Eyes *or* Unit of randomization/ unit of analysis	• **One eye included in study**, *specify how eye selected* • **Two eyes included in study, both eyes received same treatment**, *briefly specify how* analyzed*(best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within-person correlation) and specify if mixture one eye and two eyes* • **Two eyes included in study, eyes received different treatments,***specify if correct pair-matched analysis done*	How were missing data handled? *e.g. available-case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Participants		
Country		Setting
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are reported only for the people who were followed up, please indicate.*	Ethnic group/ancestry
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =) ***See MECIR 65 and 70***	• Number of people randomized to this group • Drug (or intervention) name • Dose • Frequency • Route of administration	
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up

CONTRIBUTIONS OF AUTHORS

Each author of the protocol has contributed to the following tasks.

- Conception and design of the protocol: AB, JR, SP
- Drafting the protocol or commenting on it critically for intellectual content: AB, JR, SP
- Final approval of the document to be published: AB, JR, SP

DECLARATIONS OF INTEREST

Sheel R Patel: None known.
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INDEX TERMS

Medical Subject Headings (MeSH)

*Lymphangioma [drug therapy] [surgery]; *Orbital Neoplasms [drug therapy] [surgery]; Antibiotics, Antineoplastic [therapeutic use]; Treatment Outcome

MeSH check words

Humans